

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

## IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.



03-20-02

0430

DPSO  
APR 12 2002

EXPRESS MAIL #

EU 091543335 US

DATE MAILED: MARCH , 2002

In re: Application of: MICHAEL A. MURPHY

S/N 10/017,235

For: COMPOSITION, SYNTHESIS AND THERAPEUTIC APPLICATIONS OF POLYAMINES

Docket No. 1865.1-4

Contents: PRIOR ART STATEMENT AND 186 REFERENCE COPIES, WITH TRANSMITTAL

I hereby certify that the above-listed papers are being deposited in the UNITED STATES POSTAL SERVICES as EXPRESS MAIL.

POST OFFICE TO ADDRESSEE:

BOX PRIOR ART STATEMENTS  
ASSISTANT COMMISSIONER  
OF PATENTS  
WASHINGTON, D.C. 20231

on the date and under the mailing label number indicated above.

Registered Representative: JOHN D. BUCHACA

Registration No: 37,289

Date: MARCH 19, 2002

ltrs&gt;EXPMAIL.TRA

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.W./

Please type a plus sign (+) inside this box →

PTO/SB/08A (10-96)

**Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE**



Substitute for form 1449A/PTO

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

Sheet 1 of 30

<i>Complete if Known</i>	
<b>Application Number</b>	10/017,235
<b>Filing Date</b>	December 18, 2001
<b>First Named Inventor</b>	MICHAEL A. MURPHY
<b>Group Art Unit</b>	Unknown
<b>Examiner Name</b>	Unknown
<b>Attorney Docket Number</b>	1865-1-4

## U.S. PATENT DOCUMENTS

## FOREIGN PATENT DOCUMENTS

Examiner Signature	/Paul Ward/ (03/15/2009)	Date Considered
--------------------	--------------------------	-----------------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup>Unique citation designation number. <sup>2</sup>See attached Kinds of U.S. Patent Documents. <sup>3</sup>Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup>For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup>Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup>Applicant is to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231.  
**DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO:** Assistant Commissioner for Patents, Washington, DC 20231

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.W./

### References Cited

- Abraham A.S. Brooks B.A., Elylath U. The effects of chromium supplementation on serum glucose and lipids in patients with and without non-insulin-dependent diabetes. *Metabolism: Clin. Exper.* (1992) Jul, 41(7):768-71.
- Abraham C.R., Driscoll J., Potter H., Van Nostrand W.E., Tempst P. A calcium-activated protease from Alzheimer's disease brain cleaves at the N-terminus of the amyloid B-protein. *Biochem. Biophys. Res. Commun.* (1991), 174, 790 - 96.
- Abraham C.R., Razzaboni B.L., Sisodia S.S., Koo E.H., Price D.L., Van Nostrand W.E., Papastotysis G. Studies on the proteolytic degradation of the B-protein precursor by proteases purified from Alzheimer's brain. *Ann. New York Acad. Sci.* (1991), 640, 161 - 65.
- Abraham C.R., Razzaboni B.I., Papastotysis G., Picard E., Kanemaru K., Meckelein B., Mucke L. Purification and cloning of brain proteases capable of degrading the B-amyloid precursor protein. *Ann. New York Acad. Sci.* (1992) 674, 174 - 179.
- Akkan A.G., Malaisse W.J. Iterative pulse administration of succinic acid monomethyl ester to streptozotocin diabetic rats. *Diabetes Res.* (1993), 23(2):55-63.
- Aldrich, P., Hermann, E.C., Meier, W. E., Antiviral Agents. Structure-Activity Relationships of Compounds Related to 1-Adamantanamine, *Jour. Med. Chem.*, (1971), 14, 535-543.
- Anand-Srivastava M.B., McNeill J.H. Yang X.P. Reversal of defective G-proteins and adenyl cyclase/cAMP signal transduction in diabetic rats by vanadyl sulphate therapy. *Molec. Cell. Biochem.* (1995), Dec 6-20, 153(1-2):113-9.
- Arbustini, E; Diegoli, M; Fasani, R; Grasso, M; Morbini, P; Banchieri, N; Bellini, O; Dal Bello, B; Pilotto, A; Magrini, G; Campana, C; Fortina, P; Gavazzi, A; Narula, J; Vigano, M. Mitochondrial DNA mutations and mitochondrial abnormalities in dilated cardiomyopathy. *Amer. Jour. Path.* (1998), Nov, 153(5), 1501-10.
- Arbustini, E; Morbini, P; Pilotto, A; Gavazzi, A; Tavazzi, L. Genetics of idiopathic dilated cardiomyopathy. *Herz* (2000), May, 25(3), 156-60.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.W./

Baeza I., Ibanez M, Wong C., Chavez P., Gariglio P. Possible prebiotic significance of polyamines in the condensation, protection, encapsulation, and biological properties of DNA. *Orig. Life Evol. Spec.* (1992), 21, 225 - 42.

Barefield, K., Wagner, F., Metal Complexes of 1,4,8,11-Tetramethyl-1,4,8,11-tetraazacyclotetradecane, N-Tetramethylcyclam, *Inorg. Chem.*, (1973), 12, 2435-2436.

Barefield, E.K., Wagner, F., Hodges, K.D., Synthesis of Macrocyclic Tetramines by Metal Ion Assisted Cyclization Reactions. *Inorg. Chem.*, (1976), 15, 1370-1377.

Barrera-Hernandez G., Wanke I.E., Wong N.C. Phlorizin or vanadate treatment reverses impaired expression of albumin and hepatocyte nuclear factor 1 in diabetic rats. *Diabetes* (1996), Sep, 45(9):1217-22.

Barrett, G.M., et al., Dissolving Metal Reduction of Esters to Alkanes. *Jour. Chem. Soc., Perkin I*, (1981), 1501-1509.

Beneviste M., Mayer M.L. Multiple effects of spermine on n-methyl-D-aspartic acid receptor responses of rat cultured hippocampal neurons. *Jour. Physiol.* (1993), 464, 131 - 63.

Black R.A., Kronheim S., Merriam J., March C., Hopp T.A. Preaspartate protease from human leukocytes that cleaves pro-interleukin-1B. *Jour. Biol. Chem.* (1989), 264, 5323 - 26.

Blomgren K., Nilsson E., Karlsson J. Calpain and calpastatin levels in different organs of the rabbit. *Compar. Biochem. Physiol. B*. (1989), 93, 403 - 07.

Bonte, CA; Matthijs, GL; Cassiman, JJ; Leys, AM. Macular pattern dystrophy in patients with deafness and diabetes. *Retina* (1997), 17(3):216-21.

Bradley W.G., Krasin F. A new hypothesis of the etiology of amyotrophic lateral sclerosis. *Arch. Neurol.* (1982), 39, 677 - 80.

Borthwick, GM; Johnson, MA; Ince, PG; Shaw, PJ; Turnbull, DM. Mitochondrial enzyme activity in amyotrophic lateral sclerosis: implications for the role of mitochondria in neuronal cell death. *Ann. Neurol.* (1999), Nov, 46(5):787-90.

Brabenboer B., Kappelle A.C. Harmers F.P.T., van Buren T., Erkelens D.W., Gispen W.H. Potential use of glutathione for the prevention and treatment of diabetic neuropathy in the streptozotocin-induced diabetic rat. *Diabetologia* (1992), 35, 813 - 17.

Brantl V., Gramsch C., Lottspeich F., Henschen A., Jager R.A., Herz A. Novel opioid peptides derived from mitochondrial cytochrome b: cytocrinins. *Eur. Jour. Pharmacol.* (1985), III, 293 - 94.

Bu, X, Rotter, J.I. Wolfram syndrome: a mitochondrial-mediated disorder? *Lancet*, (1993) Sep 4, 342(8871):598-600.

Bush, AI; Pettingell, WH; Multhaup, G; d Paradis, M; Vonsattel, JP; Gusella, JF; Beyreuther, K; Masters, CL; Tanzi, RE. Rapid induction of Alzheimer A  $\beta$ -amyloid formation by zinc [see comments] *Science* (1994), Sep 2, 265(5177):1464-7.

Cam M.C., Rodrigues B., McNeill J.H. Distinct glucose lowering and beta cell protective effects of vanadium and food restriction in streptozotocin-diabetes. *Eur. Jour. Endocrin.* (1999), Nov, 141(5):546-54.

Cam M.C., Pederson R.A., Brownsey R.W., McNeill J.H., Long-term effectiveness of oral vanadyl sulphate in streptozotocin-diabetic rats. *Diabetologia* (1993), 36, 218 - 24.

Cam M.C. Brownsey, RW, McNeill, JH. Mechanisms of vanadium action: insulin-mimetic or insulin-enhancing agent? *Can. Jour. Physiol. Pharmacol.* (2000) Oct, 78(10):829-47.

Cameron N.E., Cotter M.A., Maxfield E.K. Anti-oxidant treatment prevents the development of peripheral nerve dysfunction in streptozotocin-diabetic rats. *Diabetologia* (1993), 36, 299 - 304.

Cameron N.E., Cotter M.A., Archoibald V., Dines K.C., Maxfield E.K., Anti-oxidant and Pro-oxidant effects on nerve conduction velocity, endoneurial blood flow and oxygen tension in non-diabetic and streptozotocin-diabetic rats. *Diabetologia* (1994), 37, 449 - 59.

Cavanaugh P.F., Pavelic Z. P., Porter C.W. enhancement of 1,3-Bis(2-chloroethyl)-1-nitrosurea-induced cytotoxicity and DNA damage by  $\beta$ -difluoromethylornithine in L1210 leukemia cells. *Cancer Res.* (1984), 44, 3856 - 61.

Chakrabarti A.K., Banik N., Powers J., Hogan E. The regional and subcellular distribution of calcium activated neutral proteinase (CANP) in the bovine central nervous system. Neurochem. Res. (1989), 14, 259 - 66.

Chen H., Carlson EC., Pellet L., Moritz, J.T., Epstein P.N. Overexpression of metallothionein in pancreatic beta-cells reduces streptozotocin-induced DNA damage and diabetes. Diabetes 2001 Sep, 50(9):2040-6.

Chen J., Jin K., Chen M., Pei W., Kawaguchi K., Greenberg D.A., Simon R.P. early detection of DNA strand breaks in the brain after focal transient ischemia: implications for the role of DNA damage in apoptosis and neuronal cell death. Jour. Neurochem. (1997), 69, 232 - 45.

Chen, SJ; Bradley, ME; Lee, TC. Chemical hypoxia triggers apoptosis of cultured neonatal rat cardiac myocytes: modulation by calcium-regulated proteases and protein kinases. Molec. Cellul. Biochem. (1998), Jan, 178(1-2), 141-9.

Chu P., CC; Huang, CC; Fang, W; Chu, NS; Pang, CY; Wei, YH. Peripheral neuropathy in mitochondrial encephalomyopathies. Eur. Neurol. (1997), 37(2):110-15.

Chu P., Saito H., Abe K. Polyamines promote regeneration of injured axons of cultured rat hippocampal neurons. Brain Res. (1995), 673, 233- 41.

Clark, A; de Koning, EJ; Hattersley, AT; Hansen, BC; Yajnik, CS; Poulton, J. Pancreatic pathology in non-insulin dependent diabetes (NIDDM). Diabetes Res. Clin. Prac. (1995), Aug, 28 Suppl., S39-47.

Clayton D.A., Doda J.N., Friedberg E.C. The absence of a pyrimidine dimer repair mechanism in mammalian mitochondria. Proc. Natl. Acad. Sci. (1974), 71, 2777 - 81.

Clopath P., Smith V.C., McCully K.S. Growth promotion by homocysteic acid. Science (1976), 373 - 74.

Cohen N., Halberstam M., Shlimovich P., Chang C.J., Shamoon H., Rossetti L. Oral vanadyl sulfate improves hepatic and peripheral insulin sensitivity in patients with non-insulin-dependent diabetes mellitus. Jour. Clin. Invest. (1995), Jun, 95(6):2501-9.

Comi, GP; Bordoni, A; Salani, S; Franceschina, L; Sciacco, M; Prelle, A; Fortunato, F; Zeviani, M; Napoli, L; Bresolin, N; Moggio, M; Ausenda, CD; Taanman, JW; Scarlato, G. Cytochrome c oxidase subunit I microdeletion in a patient with motor neuron disease. *Ann.Neurol.* (1998), Jan, 43(1):110-6.

Corral-Debrinski, M; Shoffner, JM; Lott, MT; Wallace, DC. Association of mitochondrial DNA damage with aging and coronary atherosclerotic heart disease. *Mutat. Res.* (1992), Sep, 275(3-6), 169-80.

Corral-Debrinski M. Mitochondrial DNA deletions in human brain: regional variability and increase with advanced age. *Nat. Genet.* (1992), Dec;2(4):324-9.

Corral-Debrinski, M; Horton, T; Lott, MT; Shoffner, JM; McKee, AC; Beal, MF; Graham, BH; Wallace, DC. Marked changes in mitochondrial DNA deletion levels in Alzheimer brains. *Genomics* (1994), Sep 15, 23(2):471-6.

Cotter M.A., Cameron N.E. Neuroprotective effects of carvidilol in diabetic rats, prevention of defective peripheral nerve perfusion and conduction velocity. *Nauyn Schmiedbergs Arch. Pharmacol.* (1995), 351, 630 - 35.

Craven P.A., DeRubertis F.R., Kagan V.E., Melhem M., Studer R.K., Effects of supplementation with vitamin C or E on albuminuria, glomerular TGF- $\beta$ 1 and glomerular size in diabetes. *Jour. Amer. Soc. Nephrol.* (1997), 8, 1405 - 11.

Cui, J; Holmes, EH; Greene, TG; Liu, PK. Oxidative DNA damage precedes DNA fragmentation after experimental stroke in rat brain. *Faseb Journal* (2000) May, 14(7):955-67.

Dawson G., Glaser P. Apparent cathepsin B deficiency in neuronal ceroid lipofuscinosis can be explained by peroxide inhibition. *Biochem. Biophys. Res. Commun.* (1987), 147, 267 - 74.

Dawson G., Glaser P. Abnormal cathepsin B activity in Batten's disease. *Amer. Jour. Med. Genet. Suppl.* (1988), 5, 209 - 20.

Domingo J.L., Gomez M., Sanchez D.J., Llobet JM., Keen, C.L. Toxicology of vanadium compounds in diabetic rats: the action of chelating agents on vanadium accumulation. *Molec. Cell. Biochem.* (1995), Dec 6-20, 153(1-2):233-40.

Dreyer E.B., Pan Z., TORM S., Lipton S.A. Greater sensitivity of larger retinal ganglion cells to NMDA-mediated cell death. NeuroReport (1994), 5, 629 - 31.

Dreyer E.B., Zurakowski D., Schumer R.A., Podos S.M., Lipton S.A. Elevated glutamate levels in the vitreous body of humans and monkeys with glaucoma. Arch. Ophthalmol. (1996), 114, 299 - 305.

Duara R., Lopez-Alberola R.F., Barker W.W. A comparison of familial and sporadic Alzheimer's disease. Neurology. (1993), Jul;43(7):1377-84.

Dubin D.T. Evidence for conjugation between glutathione and polyamines in E. Coli. Biochem. Biophys. Res. Commun. (1959), 1 (5), 262 - 65.

Dyer G.D., Dunn J.A., Thorpe S.R., Accumulation of Maillard reaction products in skin collagen I diabetics and aging. Jour. Clin. Invest. . (1993), Jun, 91(6):2463-9.

Earle K.E., Archer A.G., Baillie, JE. Circulating and excreted levels of chromium after an oral glucose challenge: influence of body mass index, hypoglycemic drugs, and presence and absence of diabetes mellitus. Amer. Jour. Clin. Nutr. (1989), Apr, 49(4):685-9.

Ebihara I., Nakamura T., Shimada N., Koide, H. Increased plasma metalloproteinase-9 concentrations precede development of microalbuminuria in non-insulin-dependent diabetes mellitus. [Comment In: Am J Kidney Dis. (1998), Oct;32(4):669-71] Amer. Jour. Kidney Dis. (1998) Oct, 32(4):544-50.

Edelstein C., Kaiser M., Piras G., Scanu A. Demonstration that the enzyme that converts precursor of apolipoprotein A-1 is secreted by the hepatocarcinoma cell line hep G2. Arch. Biochem. Biophys. (1988), 267, 23 - 30.

Edland S.D., Silverman J., Peskind E.R., Tuan G.D., Wijsman E., Morris J.C. Increased risk of dementia in mothers of Alzheimer's disease cases: evidence for maternal inheritance. Neurology (1996), Jul;47(1):254-6.

Egawhary, DN; Swoboda, BE; Chen, J; Easton, AJ; Vince, FP. Diabetic complications and the mechanism of the hyperglycaemia-induced damage to the mt DNA of cultured vascular endothelial cells: (I) Characterization of the 4977 base pair deletion and

13 bp flanking repeats. Biochemical Soc. Trans. (1995), Nov, 23(4), 518S.

Eizirik D.L., Welsh N., Niemann A., Velloso L.A., Malaisse W.J. Succinic acid monomethyl ester protects rat pancreatic islet secretory potential against interleukin-1  $\alpha$  (IL-1  $\alpha$ ) without affecting glutamate decarboxylase expression or nitric oxide production. FEBS Lett. (1994), 337, 298 - 302.

Englander, EW; Greeley, GH Jr; Wang, G; Perez-Polo, JR; Lee, HM. Hypoxia-induced mitochondrial and nuclear DNA damage in the rat brain. Jour. Neurosci. Res. (1999), Oct 15, 58(2):262-9.

Failla, M.L., 'Kiser R.A. Altered tissue content and cytosol distribution of trace metals in experimental diabetes. Jour. Nutr. (1981), Nov, 111(11):1900-9.

Fantus I.G., Tsianis E. Multifunctional actions of vanadium compounds on insulin signaling pathways: evidence for preferential enhancement of metabolic versus mitogenic effects. Molec. Cell Biochem. (1998), May 182(1-2):109-19.

Fawcett, T.G., Rudich, S.M., Toby, B.H., LaLancette, R.A., Potenza, J.A., Schugar, H.J. Studies of Chelation Therapy. Inorg. Chem. (1980), 19, 940.

Ferrari, R. The role of mitochondria in ischemic heart disease. Jour. Cardiovasc. Pharmacol. (1996), 28 Suppl 1, S1-10.

Fischer, H.R., Hodgson, D.J., Michelsen, K., Pedersen, E., Synthesis and Characterization of the Dimeric Cr(III) Complex Di--hydroxobis[N,N'-bis(2-pyridylmethyl)-1,3-propanediamine]chromium (III)] Perchlorate, Inorg. Chim. Acta, (1984), 88, 143-150.

Freiberg J.M., Schneider T.R., Streeten D.H.A. Effect of Brewer's yeast on glucose tolerance. Ann. Meeting Amer. Diab. Assoc. (1975) Abstract.

Gai W.P., Blumbergs P.C., Blesing W.W. The ultrastructure of Lewy neurites. Mov. Disord. (1977), 12, Suppl.1:5.

Gerbitz, KD. Does the mitochondrial DNA play a role in the pathogenesis of diabetes? Diabetologia (1992), Dec, 35(12), 1181-6.

Gilad G., Dornay M., Gilad V. Polyamines induce precocious development in rats. Possible interaction with growth factors. Int. Jour. Devl. Neurosci. (1989), 7(6), 641 - 53.

Goering P.L., Tandon S.K., Klaassen C.D. Induction of hepatic metallothionein in mouse liver following administration of chelating agents. Toxicol. Appl. Pharmacol. (1985), 80, 467 - 72.

Goldfine A.B., Simonson D.C., Folli F., Patti, ME., Kahn C.R. In vivo and in vitro studies of vanadate in human and rodent diabetes mellitus. Molec. Cell. Biochem. (1995) Dec 6-20, 153(1-2):217-31.

Goldfine A.B., Patti M.E., Zuberi L., Goldstein B.J., LeBlanc R., Landaker E.J., Jiang Z.Y., Willsky G.R., Kahn C.R.. Metabolic effects of vanadyl sulfate in humans with non-insulin-dependent diabetes mellitus: in vivo and in vitro studies. Metabolism: Clin. Experim. (2000) Mar, 49(3):400-10.

Golub, G., Cohen, H., Meyerstein, D., The Stabilization of Monovalent Copper Ions by Complexation with Saturated Tertiary Amine Ligands in Aqueous Solutions. Jour. Chem. Soc., Chem. Commun., (1992), 397-398.

Goodwin, H.A., Lions, F., Quadridentate Chelate Compounds, Jour. Amer. Chem. Soc., (1960), 82, 5013-5023.

Goodman Y., Bruce A.J., Cheng B., Mattson M.P., Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury and amyloid  $\beta$ -peptide toxicity in hippocampal neurons. Jour. Neurochem. (1996), 66, 1836 - 44.

Grankvist, K; Marklund, SL. Opposite effects of two metal-chelators on alloxan-induced diabetes in mice. Life Sci. (1983), Dec 19, 33(25):2535-40.

Hagglof B., Hallmans G., Holmgren G., Ludvigsson J., Falkmer S. Prospective and retrospective studies of zinc concentration in serum, blood clots, hair and urine in young patients with insulin-dependent diabetes mellitus. Acta Endocrin. (Copenh) (1983), 102, 88 - 95.

Haglund, B; Ryckenberg, K; Selinus, O; Dahlquist, G. Evidence of a relationship between childhood-onset type I diabetes and low groundwater concentration of zinc. Diabetes Care 1996 Aug, 19(8):873-5.

Hamakubo T., Kannagi R., Murachi T., Matus A. Distribution of calpain I and II in rat brain. Jour. Neurosci. (1986), 6, 3103 - 11.

Hambidge, KM; Rodgerson, DO; O'Brien, D. Concentration of chromium in the hair of normal children and children with juvenile diabetes mellitus. Diabetes 1968 Aug, 17(8):517-9.

Hay, R.W., Gidney, P.M., Lawrence, G.A., Cobalt Complexes of 3,7-Dithianonane-1,9-diamine. Jour. Chem. Soc., Dalton, (1975), 779-784.

Heyliger C.E., Tahiliani A.G., McNeill J.H.. Effect of vanadate on elevated blood glucose and depressed cardiac performance of diabetic rats. Science (1985), Mar 22, 227(4693):1474-7.

Husain S., Hadi S.M. Strand scission in DNA induced by L-DOPA in the presence of Cu(II). FEBS Lett. (1995), 364, 75 - 78.

Husain S., Hadi S.M. DNA breakage by L-DOPA and Cu(II): breakage by melanin and bacteriophage inactivation. Mutat. Res. (1998), 397, 161 - 68.

Isobe, K; Ito, S; Hosaka, H; Iwamura, Y; Kondo, H; Kagawa, Y; Hayashi, JI. Nuclear-recessive mutations of factors involved in mitochondrial translation are responsible for age-related respiration deficiency of human skin fibroblasts. Jour. Biol. Chem. (1998), Feb 20, 273(8):4601-6.

Jiang Z.Y., Zhou Q.L., Eaton J.W., Koppenol W.H., Hunt J.V., Wolff S.P. Spirohydantoin inhibitors of aldose reductase inhibit iron- and copper-catalysed ascorbate oxidation in vitro. Biochem. Pharmacol. (1991), Aug 22, 42(6):1273-8.

Johns, DR, Sadun, AA, Cuban epidemic optic neuropathy. Mitochondrial DNA analysis. Jour. Neuro-Ophthalmol., (1994), Sep, 14(3):130-4.

Karasu C., Dewhurst M., Stevens E.J., Tomlinson D.R., Effects of anti-oxidant treatment on sciatic nerve dysfunction in streptozotocin-diabetic rats; comparison with essential fatty acids. Diabetologia (1995), 38, 129 - 34.

Kelner M.J., Bagnell R., Hale B., Alexander N.M. Inactivation of intracellular copper-zinc superoxide dismutase by chelating agents without glutathione depletion and methemoglobin formation. Free Radical Biol. Med. (1989), 6 (4), 355 - 60.

Khan A.U. , DiMascio P., Medeiros M. H., Wilson T. Spermine and spermidine protect ion of plasmid DNA against single-strand breaks induced by singlet oxygen. Proc. Natl. Acad. Sci. (1992), 89, 11428 - 30.

Kinlaw W.B., Levine A.S., Morley J.E., Silvs S.E., McClain C.J. Abnormal zinc metabolism in type II diabetes mellitus. Amer. Jour. Med. (1983), 75, 273 - 7.

Kodama, H; Murata, Y; Itsuka, T; Abe, T. Metabolism of administered triethylene tetramine dihydrochloride in humans. Life Sciences, (1997), 61(9):899-907.

Kooistra T., Van Hinsbergh V., Havekes L., Jan Kempen H. In vitro studies on origin and site of action of enzyme activity responsible for conversion of human proapo protein A-1 into apo protein A-1. FEBS Lett. (1984), 170, 109 - 13.

Kristal B.S., Koopmans S.J., Jackson Y., Ikeno B.J., Park B.J., Yu B.P. Oxidant-mediated repression of mitochondrial transcription in diabetic rats. Free Radical Biol. Med. (1997), 813 - 22.

Kruman, II; Culmsee, C; Chan, SL; Kruman, Y; Guo, Z; Penix, L; Mattson, M.P. Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity. Journal of Neuroscience (2000), Sep 15, 20(18):6920-26.

Krumkalns, E.V., Pfeifer, W., Adamantylamines by Direct Amination of 1-Bromoadamantane, Jour. Med. Chem., (1968), 11, 1103.

Langsjoen, PH; Folkers, K; Lyson, K; Muratsu, K; Lyson, T; Langsjoen, P. Effective and safe therapy with coenzyme Q10 for cardiomyopathy. Klinische Wochenschrift (1988), Jul 1, 66(13):583-90.

Leclercq-Meyer V., Malaisse W.J., Enhancement by succinic acid dimethyl ester of insulin release evoked by D-glucose and glimepiride in the perfused pancreas of normoglycemic and hyperglycemic rats. Biochem. Pharmacol. (1993), 47, 1519 - 24.

Lee T.S., Saltsman K.A., Ohashi H. Activation of protein kinase C by elevation of glucose concentration: proposal for a mechanism in the development of diabetic vascular complications. Proc. Natl. Acad. Sci. (1989), Jul; 86(13):5141-5.

Lee, HK; Song, JH; Shin, CS; Park, DJ; Park, KS; Lee, KU; Koh, CS. Decreased mitochondrial DNA content in peripheral blood precedes the development of non-insulin-dependent diabetes mellitus. *Diabetes Res.Clin. Prac.* (1998) Dec, 42(3):161-7.

Levay G., Ye Q., Bodell W.J. Formation of DNA adducts and oxidative base damage by copper mediated oxidation of dopamine and 6-hydroxydopamine. *Exper. Neurol.* (1997), 146, 570 - 74.

Lovell M.A., Robertson J.D., Teesdale W.J., Campbell J.L., Markesberry W.R. Copper, iron, and zinc in Alzheimer's disease senile plaques. *Jour . Neur. Sci.* (1998), 158, 47 - 52.

Lynch J.J. Ferro T.J., Blumenstock F.A. Increased endothelial albumin permeability mediated by protein kinase C activation. *Jour. Clin. Invest.* (1990), Jun;85(6):1991-98.

Low, PA; Nickander, KK; Tritschler, HJ. The roles of oxidative stress and antioxidant treatment in experimental diabetic neuropathy. *Diabetes* (1997), Sep, 46 Suppl 2:S38-42.

MacDonald M.J., Fahien L.A. Glyceraldehyde phosphate and methyl esters of succinic acid. Two "new" potent insulin secretagogues. *Diabetes*. (1988), Jul;37(7):997-9.

Malaisse W.J., Sener A. Metabolic effects and fate of succinate esters in pancreatic islets. *Amer. Jour. Physiol.*(1993), Mar;264(3 Pt 1):E434-40.

Malaisse W.J., Rasschaert J., Villaneuva-Penacarrillo M.I., Valverde I. Respiratory, ionic, and functional effects of succinate esters in pancreatic islets. *Amer. Jour. Physiol.* (1993), Mar;264(3 Pt 1):E428-33.

Malaisse, WJ. The  $\square$  cell in NIDDM: giving light to the blind. *Diabetologia* (1994), Sep, 37 Suppl 2:S36-42.

Matus A., Green G. Age-related increase in a cathepsin D like protease that degrades brain microtubule-associated proteins. *Biochemistry* (1987), 26, 8083 - 86.

Maechler, P; Wollheim, CB. Mitochondrial signals in glucose-stimulated insulin secretion in the  $\square$  cell. *Jour. Physiol.* (2000) Nov 15, 529 Pt 1:49-56.

Maedler, K; Spinas, GA; Dyntar, D; Moritz, W; Kaiser, N; Donath, MY. Distinct effects of saturated and monounsaturated fatty acids on  $\beta$ -cell turnover and function. *Diabetes* (2001), Jan, 50(1):69-76.

Marin-Garcia, J; Goldenthal, MJ; Ananthakrishnan, R; Pierpont, ME. The complete sequence of mtDNA genes in idiopathic dilated cardiomyopathy shows novel missense and tRNA mutations. *Jour. Card. Fail.* (2000), Dec, 6(4), 321-9.

Mateo M.C.M., Bustamante J.B., Cantalapiedra M.A.G. Serum zinc, copper and insulin in diabetes mellitus. *Biomed.* (1978), 29, 56 - 58.

Mattson, MP; Culmsee, C; Yu, ZF. Apoptotic and antiapoptotic mechanisms in stroke. *Cell Tissue Res.* (2000), Jul, 301(1):173-87.

McCance D.R., Dyer D.G., Dunn J.A., Bailie K.E., Thorpe S.R., Baynes J.W., Lyons T.J. Maillard reaction products and their relation to complications in insulin-dependent diabetes mellitus. *Jour. Clin. Invest.* (1993), Jun 91(6):2470-8.

McCully K.S. Homocysteine metabolism in scurvy, growth and arteriosclerosis. *Nature* (1971), 23, 391 - 92.

McCully K.S., Vezeridis M.P., Histopathological effects of homocysteine thiolactone on epithelial and stromal tissues. *Exp. Molec. Pathol.* (1989), 51, 159 - 70.

McCully K.S., Olszewski A.J., Vezeridis M.P. Homocysteine and lipid metabolism in atherogenesis: effect of the homocysteine thiolactonyl derivatives, thioretinaco and thioretinamide. *Atherosclerosis* (1990), Aug, 83(2-3):197-206.

McCully, K.S. Tzanakakis G.N., Vezeridis M.P. Effect of the synthetic N-homocysteine thiolactonyl derivatives, thioretinaco, thioretinamide, and thioco on growth and lactate production by malignant cells. *Res. Commun. Chem. Pathol. Pharmacol.* (1992), Jul, 77(1):125-8.

McCully K.S. Chemical pathology of homocysteine. III. Cellular function and aging. *Ann. Clin. Lab. Sci.* (1994a), Mar-Apr, 24(2):134-52.

McCully, KS. Chemical pathology of homocysteine. II. Carcinogenesis and homocysteine thiolactone metabolism. Ann. Clin. Lab. Sci. (1994b), Jan-Feb, 24(1):27-59.

McGurk J.F., Bennett M.V., Zukin R.S. Polyamines potentiate responses of N-methyl-D-aspartate receptors expressed in Xenopus oocytes. Proc. Natl. Acad. Sci. (1990), 87, 9971 - 74.

McLaren G.D. Muir WA. Kellermeyer R.W. Iron overload disorders: natural history, pathogenesis, diagnosis and therapy. Crit. Rev. Clin. Lab. Sci. (1983), 19, 205 - 266.

Mecocci, P; Polidori, MC; Ingegnini, T; Cherubini, A; Chionne, F; Cecchetti, R; Senin, U. Oxidative damage to DNA in lymphocytes from AD patients. Neurology (1998), Oct, 51(4):1014-7.

Mecocci P., MacGarvey U., Kaufman A.E. Oxidative damage to mitochondrial DNA shows marked age dependent changes increases in human brain. Ann. Neurol (1993), 34, 609 - 16.

Mecocci, P; MacGarvey, U; Beal, MF. Oxidative damage to mitochondrial DNA is increased in Alzheimer's disease. Annals Neurol. (1994), Nov, 36(5):747-51.

Mezzetti G., Monti M.G., Moruzzi M.S... Polyamines and the catalytic domain of protein kinase C. Life Sci. (1988), 42, 2293 - 98.

Mizukami, F., Metal Complexes Containing Six-Membered Chelate Rings. The Preparation and Structure of Dichlorocobalt(III) Complexes with Tetramines Derived from 2,4-Pentanedimaine, Bull. Chem. Soc. Jpn., (1975), 48, 1205-1212.

Mikukami, F., Metal Complexes Containing Six-Membered Chelate Rings. IV. The Preparation and Structure of Dichlorocobalt(III) Complexes with Tetramines Derived from 2,4-Pentanediamine. Bull. Chem. Soc, Jpn., (1975), 48, 1205-1212.

Miyako, K; Kai, Y; Irie, T; Takeshige, K; Kang, D. The content of intracellular mitochondrial DNA is decreased by 1-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>). Jour. Biol. Chem. (1997), Apr 11, 272(15):9605-8.

Miyako, K; Irie, T; Muta, T; Umeda, S; Kai, Y; Fujiwara, T; Takeshige, K; Kang, D. 1-Methyl-4-phenylpyridinium ion (MPP<sup>+</sup>) selectively inhibits the replication of mitochondrial DNA. Eur. Jour. Biochem. (1999), Jan, 259(1-2):412-8.

de la Monte, SM; Luong, T; Neely, TR; Robinson, D; Wands, JR. Mitochondrial DNA damage as a mechanism of cell loss in Alzheimer's disease. *Lab. Invest.* (2000), Aug, 80(8):1323-35.

Morgan J.M. Hepatic chromium content in diabetic subjects. *Metabolism: Clin. Exper.* (1972), Apr, 21(4):313-6.

Moruzzi M.S., Monti M.G., Piccinini G., Marverti G., Tadolini B. Effect of spermine on association of protein kinase C with phospholipid vesicles. *Life Sci.* (1990), 47(16), 1475 - 82.

Moruzzi M.S., Marverti G., Piccinini G., Frassineti C., Monti M.G. The effect of spermine on calcium requirement for protein kinase C association with phospholipid vesicles. *International Jour. Biochem. Cell Biol.* (1995), 27(8), 783 - 8.

Moruzzi M.S., Piccinini G., Tadolini B., Monti M.G., Barbiroli B., Mezzetti G. In: *Progress in polyamine research. Effect of polyamines on protein kinase C activation process*. *Adv. Exp. Med. Biol.* (1988), 250:469-80.

Moustaid N., Sul H.S., Regulation of expression of the fatty acid synthase gene in 3T3-L1 cells by differentiation and triiodothyronine. *Jour. Biol. Chem.* (1991), 18550 - 554.

Naviaux, RK. Mitochondrial DNA disorders. *Eur. Jour. Ped.* (2000), Dec, 159 Suppl 3:S219-26.

Noto R., Alicata R., Sfogliano L. A study of cupremia in a group of elderly diabetics. *Acta Diabetol. Latina* (1983), 20, 81- 85.

Oberholzer, M.R., Neuburger, M., Zehnder, M., Kaden, T.A., Steric Effects in the Cu(II) and Ni(II) Complexes with Tetra-N-alkylated 1,4,8,11-Tetraazacyclotetradecanes. *Helv. Chim Acta*, (1995), 78, 505.

Odawara, M; Yamashita, K. Mitochondrial gene abnormalities and  $\square$ - and  $\square$ -cell dysfunction. *Diabetes Care* (1996), Oct, 19(10):1166-7.

Oka Y., Katagiri H., Yazaki Y., Murase T., Kobayashi T. Mitochondrial gene mutation in islet-autoantibody-positive patients who were initially non-insulin-dependent diabetics. *Lancet* (1993), 342, 527 - 28.

Oka, Y.NIDDM--genetic marker; glucose transporter, glucokinase, and mitochondria gene. *Diabetes Res. Clin. Prac.* (1994), Oct, 24 Suppl., S117-21.

Ozawa, T. Mitochondrial DNA mutations in myocardial diseases. *European Heart Journal* (1995), Dec, 16 Suppl O, 10-14.

Ozawa, T; Hayakawa, M; Katsumata, K; Yoneda, M; Ikebe, S; Mizuno, Y. Fragile mitochondrial DNA: the missing link in the apoptotic neuronal cell death in Parkinson's disease. *Biochem. Biophys. Res. Commun.* (1997), Jun 9, 235(1):158-61.

Olszewski A.J., McCully K.S. Homocysteine metabolism and the oxidative modification of proteins and lipids. *Free Rad. Biol. Med.* (1993), Jun, 14(6):683-93.

Papadopoulou, LC; Theophilidis, G; Thomopoulos, GN; Tsiftsoglou, AS. Structural and functional impairment of mitochondria in adriamycin-induced cardiomyopathy in mice: suppression of cytochrome c oxidase II gene expression. *Biochem. Pharmacol.* (1999), Mar 1, 57(5):481-9.

Park, KS; Lee, KU; Song, JH; Choi, CS; Shin, CS; Park, DJ; Kim, SK; Koh, JJ; Lee, HK. Peripheral blood mitochondrial DNA content is inversely correlated with insulin secretion during hyperglycemic clamp studies in healthy young men. *Diabetes Res. Clin. Prac.* (2001), May, 52(2):97-102.

Perlmutter L.S., Siman R., Gall C., Seubert P., Lynch G. The ultrastructural localization of calcium- activated protease "calpain" in rat brain. *Synapse* (1988), 2, 78 - 88.

Press E.M., Porter R., Cebra J. The isolation and properties of a proteolytic enzyme, cathepsin D, from bovine spleen. *Biochem. Jour.* (1960), 74, 501 - 14.

Quigley H.A. Ganglion cell death in glaucoma: Pathology recapitulates ontogeny. *Aust. NZ J. Ophthalmol.* (1995), 23, 85 - 91.

Razzaboni B.L., Papastoitsis G., Koo E.H., Abraham C.R., A calcium-stimulated serine protease from monkey brain degrades the B-amyloid precursor protein. *Brain Res.* (1992), 589, 207 - 16.

Reul, B.A., Amin S.S., Buchet, J.P., Ongemba L.N., Crans D.C., Brichard S.M. Effects of vanadium complexes with organic ligands

on glucose metabolism: a comparison study in diabetic rats.  
Brit. Jour. Pharmacol. (1999) Jan, 126(2):467-77.

Rose C., Camus A., Schwartz J.C. A serine peptidase responsible for the inactivation of endogenous cholecystokinin in brain. Proc. Natl. Acad. Sci. (1988), 85(21), 8326 - 30.

Rose C., Camus A., Schwartz J. Protection by serine peptidase inhibitors of endogenous cholecystokinin released from brain slices. Neuroscience (1989), 29 (3), 583 - 94.

Sadun, A. Acquired mitochondrial impairment as a cause of optic nerve disease. Trans. Amer. Ophthalmol. Soc. (1998), 96:881-923.

Scanu A.M. Proapolipoprotein-converting enzymes and high density lipoprotein early events in biogenesis. Amer. Heart Jour. (1987), 113, 527 - 33.

Schapira, AH. Evidence for mitochondrial dysfunction in Parkinson's disease--a critical appraisal. Movement Disorders (1994), Mar., 9(2):125-38.

Schapira, AH. Mitochondrial dysfunction in neurodegenerative disorders. Biochim. Biophys. Acta (1998), Aug 10, 1366(1-2):225-33.

Schmitz C; Axmacher B; Zunker U; Korr H. Age-related changes of DNA repair and mitochondrial DNA synthesis in the mouse brain. Acta Neuropath. (1999), Jan, 97(1):71-81.

Schroeder H.A. Cadmium, chromium, and cardiovascular disease. Circulation 1967 Mar, 35(3):570-82.

Schroeder H.A. Chromium deficiency as a factor in atherosclerosis. Jour. Chronic Dis. (1970), 23, 123 - 42.

Seidman MD; Khan MJ; Bai U; Shirwany N; Quirk WS. Biologic activity of mitochondrial metabolites on aging and age-related hearing loss. Amer. Jour. Otol. (2000), Mar, 21(2):161-7.

Serradas P., Girox M.H., Saulnier C., Mitochondrial deoxyribonucleic acid content is specifically decreased in adult but not fetal pancreatic islets of the Goto-Kakizaki rat, a genetic model of insulin-dependent diabetes. Endocrinology (1995), 136, 5623 - 31.

Shoffner, JM; Brown, MD; Torroni, A; Lott, MT; Cabell, MF; Mirra, SS; Beal, MF; Yang, CC; Gearing, M; Salvo, R; et al. Mitochondrial DNA variants observed in Alzheimer disease and Parkinson disease patients. *Genomics* (1993), Jul, 17(1):171-84.

Smith M.A., Harris P.L., Sayre L.M., Perry G. Iron Accumulation in Alzheimer's disease is a source of redox-generated free radicals. *Proc. Natl. Acad. Sci.* (1997), 94, 9866 - 9868.

Snyder R.D. Inhibition of X-ray-induced DNA strand break repair in polyamine depleted HeLa cells. *Int. Jour. Radiat. Biol.* (1989), 15(5), 773 - 79.

Soong N.W., Hinton D.R., Cortopassi G., and Arnheim N. Mosaicism for a specific somatic mitochondrial DNA mutation in adult human brain. *Nat. Genet.* (1992), Dec;2(4):318-23.

Strout H.V., Vicario P.P., Biswas C., Saperstein R., Brady E.J., Pilch P.F., Berger J. Vanadate treatment of streptozotocin diabetic rats restores expression of the insulin responsive glucose transporter in skeletal muscle. *Endocrin.* (1990), 126, 2728 - 32.

Sucher N.J., Lipton S.A., Dreyer E.B., (1997), Molecular pathology of glutamate toxicity in retinal ganglion cells. *Vision Res.* (1997), 37, 3483 - 93.

Suzuki Y., Kadokawa H., Atsumi Y., A case of diabetic amyotrophy associated with 3243 mitochondrial tRNA (Leu UUR) mutation and successful therapy with coenzyme Q10. *Endoc. Jour.* (1995), 42, 141 - 45.

Suzuki S; Hinokio Y; Komatsu K; Ohtomo M; Onoda M; Hirai S; Hirai M; Hirai A; Chiba M; Kasuga S; Akai H; Takahashi T.; Hiratani K; Kimura E., N<sub>2</sub>-Binding Mononuclear Ru(II) Tertiary Polyamine Complex, *Chemistry Letters*, (1993), 1329-1332.

Swoboda BE; Egawhary DN; Chen J; Vince FP. Diabetic complications and the mechanism of the hyperglycaemia-induced damage to the mt DNA of cultured vascular endothelial cells: (II) The involvement of protein kinase C. *Biochem. Soc. Trans.* (1995), Nov, 23(4):519S.

Tagami M., Ikeda K., Yamagata K., Nara Y., Fujino H., Kubota A., Numano F., Yamori Y. Vitamin E prevents apoptosis in hippocampal neurons caused by cerebral ischemia and reperfusion in stroke-

prone spontaneously hypertensive rats. *Lab. Invest.* (1999), 79, 609 - 15.

Tasker R.C., Sahota S.K., Cotter F.E., Williams S.R. Early post-ischemic dantrolene induced amelioration of poly(ADP-ribose) polymerase-related bioenergetic failure in neonatal rat brain slices. *Jour. Cereb. Blood Flow Metab.* (1998), 18, 1346 - 56.

Toyota, T. Oxidative damage to mitochondrial DNA and its relationship to diabetic complications. *Diabetes Res. Clin. Prac.* (1999), Sep, 45(2-3):161-8.

Trachtman H., Futterweit S., Maesake J. Taurine ameliorates chronic streptozotocin-induced diabetic nephropathy in rats. *Amer. Jour. Physiol.* (1995), 269, F429 - F438.

Tsuji A., Sakurai H. Vanadyl ion suppresses nitric oxide production from peritoneal macrophages of streptozotocin-induced diabetic mice. *Biochem. Biophys. Res. Commun.* (1996), Sep 13, 226(2):506-11.

Uemura, S; Matsushita, H; Li, W; Glassford, AJ; Asagami, T; Lee, KH; Harrison, DG; Tsao, PS. Diabetes mellitus enhances vascular matrix metalloproteinase activity: role of oxidative stress. *Circul. Res.* (2001), Jun 22, 88(12):1291-8.

Umeda S; Muta T; Ohsato T; Takamatsu C; Hamasaki N; Kang D. The D-loop structure of human mtDNA is destabilized directly by 1-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>), a Parkinsonism-causing toxin. *Eur. Jour. Biochem.* (2000), Jan, 267(1):200-6.

Uriu-Hare J.Y., Stern, J.S., Keen C.L. The effect of diabetes on the molecular localization of maternal and fetal zinc and copper metalloprotein in the rat. *Biol. Trace Element Res.* (1988), Dec, 18:71-9.

Van Alphen J. On aliphatic polyamines III. *Jour. Rec. Trav. Chim.* (1936), 55, 835 - 40.

Valera A., Rodriguez-Gil J.E., Bosch F. Vanadate treatment restores the expression of genes for key enzymes in the glucose and ketone bodies metabolism in the liver of diabetic rats. *Jour. Clin. Invest.* (1992), 92, 4 -11.

Vicent D., Villaneuva-Penacarillo M.L., Valverde I., Malaisse W.J. enhancement of the insulinotropic action of glibenclamide by succinic acid methyl esters in anaesthetized rats. *Med. Sci. Res.* (1993), 21, 517 - 18.

Wallace, D.C. Mitochondrial genetics: a paradigm for aging and degenerative diseases? *Science* (1992), May 1, 256(5057):628-32.

Wei Y.H., Kao S.H. Mitochondrial DNA mutations and lipid peroxidation in human aging. In: *Nutrients and Gene Expression*. Berdanier C.D. ed. Boca Raton FL: CRC Press, (1996); pp 165 - 88.

Whitaker J.N., Seyer J. Isolation and characterization of bovine brain cathepsin D. *Jour. Neurochem.* (1979), 32, 325 - 33.

Yang, J; Cherian, MG. Protective effects of metallothionein on streptozotocin-induced diabetes in rats. *Life Sci.* (1994), 55(1):43-51.

Yoshimoto, S; Sakamoto, K; Wakabayashi, I; Masui, H. Effect of chromium administration on glucose tolerance in stroke-prone spontaneously hypertensive rats with streptozotocin-induced diabetes. *Metabolism: Clin. Exper.*(1992), Jun, 41(6):636-42

Yu Z.F., Bruce-Keller A.J., Goodman Y., Mattson M.P. Uric acid protects neurons against excitotoxic and metabolic insults in cell culture, and against focal ischemic brain injury in vivo. *Jour. Neurosci. Res.* (1998), 53, 613 - 25.

Zeviani, M; Mariotti, C; Antozzi, C; Fratta, GM; Rustin, P; Prelli, A. OXPHOS defects and mitochondrial DNA mutations in cardiomyopathy. *Muscle and Nerve* (1995), 3, S170-4.

Zeviani M., Amati P., Comi G., Fratta G., Mariotti C., Tiranti V. Searching for genes affecting the structural integrity of the mitochondrial genome. *Biochim. Biophys. Acta* (1995), 1271, 153 - 58.